(19) World Intellectual Property Organization

International Bureau





(43) International Publication Date 19 August 2004 (19.08.2004)

(10) International Publication Number WO 2004/069284 A3

(51) International Patent Classification7: 49/18, 9/19

A61K 49/22,

(21) International Application Number:

PCT/IB2004/000243

- (22) International Filing Date: 3 February 2004 (03.02.2004)
- (25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data: 03002375.8

4 February 2003 (04.02.2003)

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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US
- of inventorship (Rule 4.17(iv)) for US only

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 25 November 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ULTRASOUND CONTRAST AGENTS AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract: Method for preparing a lyophilized matrix and, upon reconstitution of the same, a respective injectable contrast agent comprising a liquid aqueous suspension of gas-filled microbubbles stabilized predominantly by a phospholipid. The method comprises preparing an emulsion from an aqueous medium, a phospholipid and a water immiscible organic solvent. The emulsion is then freeze-dried and subsequently reconstituted in an aqueous suspension of gas-filled microbubbles. The method allows to obtain suspensions comprising microbubbles having a relatively small diameter and a narrow size distribution.



According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of ti	Relevant to claim No	
χ .	WO 99/08716 A (MARSDEN JOHN CH OMTVEIT TORE (NO); NYCOMED IMA (NO)) 25 February 1999 (1999-0 page 32, line 1 - page 33, lin	35-40	
X	EP 1 228 770 A (BRACCO RES S A 7 August 2002 (2002-08-07) page 9, line 35 - page 14, lin		35–40
Y		1-34	
X	WO 98/05364 A (MARSDEN JOHN CH BRAENDEN JORUNN (NO); DUGSTAD (NO);) 12 February 1998 (1998- page 22, line 15 - page 23, li	HARALD 02-12)	35-40
X	US 6 280 705 B1 (KLEIN DAVID H 28 August 2001 (2001-08-28) claims; examples	ET AL)	35–40
χ Furth	er documents are listed in the continuation of box C.	χ Patent family members are lis	ted in annex.
"A" documer consider affiling de "L" documer which is citation documer other m"P" documer later the	nt which may throw doubts on priority claim(s) or s cited to establish the publication date of another or other special reason (as specified) nt referring to an oral disclosure, use, exhibition or leans nt published prior to the international filing date but an the priority date claimed	 "T" later document published after the or priority date and not in conflict cited to understand the principle of invention "X" document of particular relevance; involve an inventive step when the document of particular relevance; annot be considered to involve a document is combined with one of ments, such combination being of in the art. "&" document member of the same particular after the same particul	with the application but or theory underlying the the claimed invention not be considered to e document is taken alone the claimed invention in inventive step when the r more other such docuporious to a person skilled
Date of the actual completion of the international search		Date of mailing of the international	search report
5	August 2004	22/09/2004	
Name and m	ailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni,	Authorized officer Venturini, F	

C.(Continu	ation) DOCUMENTS CO ERED TO BE RELEVANT	162004/000243
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 146 657 A (MATSUNAGA TERRY ET AL) 14 November 2000 (2000-11-14) claims; table 5	35-40
Υ	WO 96/09037 A (LIPOSOME CO INC) 28 March 1996 (1996-03-28) page 12; claims	1-34
A	WO 97/40858 A (IMARX PHARMACEUTICAL CORP) 6 November 1997 (1997-11-06) the whole document	1-40
A	SCHNEIDER M ET AL: "BR1: A NEW ULTRASONOGRAPHIC CONTRAST AGENT BASED ON SULFUR HEXAFLUORIDE-FILLED MICROBUBBLES" INVESTIGATIVE RADIOLOGY, PHILADELPHIA, PA, US, vol. 30, no. 8, 1 August 1995 (1995-08-01), pages 451-457, XP000611270 the whole document	1-40
Y	WO 99/36104 A (DU PONT PHARM CO) 22 July 1999 (1999-07-22) pages 12-19	1-34
	EP 1 419 789 A (BRISTOL MYERS SQUIBB PHARMA CO) 19 May 2004 (2004-05-19) the whole document	1-34
(US 2002/102217 A1 (HELLEBUST HALLDIS ET AL) 1 August 2002 (2002-08-01) example 11	1
	(continuation of second sheet) (January 2004)	

Information on patent family members

onal Application No
IB2004/000243

Datashilas			1B2004/000243		
Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9908716	A	25-02-1999	AU EP WO JP NO	8816198 A 1007103 A2 9908716 A2 2001515055 T 20000622 A	08-03-1999 14-06-2000 25-02-1999 18-09-2001
			ZA 	9807483 A	10-03-2000 21-05-1999
EP 1228770	Α	07-08-2002	EP	1228770 A1	07-08-2002
WO 9805364	А	12-02-1998	AU CA CN CZ EP WO IL JP JP KR	3780497 A 2262908 A1 1227502 A ,B 9900289 A3 0918546 A2 9805364 A2 128345 A 2000517296 T 2004002453 A 2000029780 A	25-02-1998 12-02-1998 01-09-1999 14-07-1999 02-06-1999 12-02-1998 24-06-2003 26-12-2000 08-01-2004
			NO NZ US	990276 A 334365 A 2002106328 A1	25-05-2000 22-01-1999 28-10-1999 08-08-2002
US 6280705	B1	28-08-2001	USSUU AAU AA CCEFHJNOLOSSSSSSUU AAU AACEPUSO	5798091 A 5605673 A 2002031476 A1 731671 B2 4922196 A 767705 B2 5199701 A 2212113 A1 1182373 A 0812214 A1 973496 A 9802095 A2 11501305 T 973489 A 321952 A1 9626746 A1 5720938 A 5626833 A 5695741 A 2004033199 A1 6287539 B1 2002028179 A1 6287539 B1 2002028179 A1 6280704 B1 694135 B2 7478294 A 8933898 A 2164813 A1 0711179 A1 9501164 T 2002098151 A1 9503835 A1	25-08-1998 25-02-1997 14-03-2002 05-04-2001 18-09-1996 20-11-2003 30-08-2001 06-09-1996 20-05-1998 17-12-1997 26-08-1997 28-01-1999 02-02-1999 27-08-1997 05-01-1998 06-09-1996 24-02-1998 06-05-1997 09-12-1997 19-02-2004 11-09-2001 07-03-2002 28-08-2001 16-07-1998 28-02-1995 14-01-1999 09-02-1995 15-05-1996 04-02-1997 25-07-2002
			US US US US	5639443 A 6372195 B1 6258339 B1 2002051750 A1	09-02-1995 17-06-1997 16-04-2002 10-07-2001 02-05-2002

information on patent family members

Ional Application No IB2004/000243

	atent document d in search report		Publication date		Patent family member(s)	Publication date
US	6280705	B1		US	2002054854 A1	
211	6146657	A	14-11-2000	110		
00	C14000/	'n	14-11-5000	US	5773024 A	30-06-1998
				US	5585112 A	17-12-1996
				US	5469854 A	28-11-1995
				US	5228446 A	20-07-1993
				US	5088499 A	18-02-1992
				US	5542935 A	06-08-1996
				US	5580575 A	03-12-1996
				US	6551576 B1	22-04-2003
				ΑT	235228 T	15-04-2003
				AT	270878 T	15-07-2004
				AU .	1004399 A	04-03-1999
				AU	2185095 A	
				AU	708341 B2	19-06-1995
				AU	3146595 A	05-08-1999
				BR		29-03-1996
					9509011 A	30-09-1997
				CA	2177713 A1	08-06-1995
				CA	2200061 A1	21-03-1996
				CN	1158082 A	,B 27-08-1997
				DE	69432358 D1	30-04-2003
				DE	69432358 T2	19-02-2004
				EP	0740528 A1	06-11-1996
				EP	0788348 A1	13-08-1997
				ĴΡ	10505900 T	09-06-1998
				ĴΡ	9506098 T	
				WO.	9515118 A1	17-06-1997
				WO		08-06-1995
					9608234 A1	21-03-1996
				US	6315981 B1	13-11-2001
				US	5733572 A	31-03-1998
				US	5922304 A	13-07-1999
				US	5705187 A	06-01-1998
				US	6088613 A	11-07-2000
			•	US	5656211 A	12-08-1997
				US	6461586 B1	08-10-2002
				US	6039557 A	21-03-2000
				ΑT	233574 T	15-03-2003
				ΑÜ	696056 B2	27_00_1000
				AU	6953794 A	27-08-1998 03-01-1005
				AU		03-01-1995
				AU ·	683900 B2	27-11-1997
					7043194 A	03-01-1995
				AU	8840698 A	04-02-1999
				CA	2164845 A1	22-12-1994
				CA	2164846 A1	22-12-1994
			•	CN	1125389 A ,	B 26-06-1996
				CN	1137748 A ´	11-12-1996
				DE	69432219 D1	10-04-2003
				DE	69432219 T2	04-12-2003
				DK	712293 T3	30-06-2003
			•	EP	1252885 A2	30-00-2003
				ĒΡ	0802788 A1	
				EP	0712293 A1	29-10-1997 22-05-1996
₩O •	 9609037		20_02_1006			
WU	JUUJUJ/	Α	28-03-1996 ·	WO Ep	9609037 A1 0783295 A1	28-03-1996 16-07-1997
WO (9740858		06-11-1997			ے ہے جانبہ تک ہیں ہے جان نے جے جانب تھ سا بھا ہے
	-, -10000	А	20-11-122/	US Au	5776429 A 2451097 A	07-07-1998 19-11-1997
				AU	/45 i NU / A	10_11_1007

Information on patent family members

onal Application No IB2004/000243

			182004/000243		
Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9740858	Α		CN	1216925 A	19-05-1999
•			EΡ	0923383 A1	23-06-1999
			JP	2000510108 T	08-08-2000
			US	6033646 A	07-03-2000
	•		WO	9740858 A1	06-11-1997
WO 9936104	 А	22-07-1999	AU	746067 B2	
		0, 1333	AU	2115599 A	11-04-2002 02-08-1999
			BR	9907066 A	04-09-2001
			CA	2317921 A1	22-07-1999
			CN	1288373 T	21-03-2001
			EΑ	2978 B1	26-12-2002
			EE	200000422 A	17-12-2001
			EP	1419789 A2	19-05-2004
			EP	1027035 A2	16-08-2000
			HR	990012 A1	31-10-1999
			HU	0100206 A2	28-06-2001
			JP	2002509121 T	26-03-2002
			NO	20003471 A	29-08-2000
			NZ	505082 A	26-11-2002
•			PL	342473 A1	04-06-2001
			SK	10312000 A3	07-11-2000
			MO	9936104 A2	22-07-1999
			US	2001003580 A1	14-06-2001
			US ZA	2004057991 A1	25-03-2004
	———— <u>—</u>			9900247 A	14-07-2000
EP 1419789	Α	19-05-2004	EP	1419789 A2	19-05-2004
			ΑU	746067 B2	11-04-2002
			AU	2115599 A	02-08-1999
			BR	9907066 A	04-09-2001
			CA	2317921 A1	22-07-1999
			CN EA	1288373 T	21-03-2001
			EE	2978 B1 200000422 A	26-12-2002
			EP	1027035 A2	17-12-2001
			HR	990012 A1	16-08-2000
			HÜ	0100206 A2	31-10-1999
·			JP	2002509121 T	28-06-2001 26-03-2002
			NO	20003471 A	29-08-2002
•			NZ	505082 A	26-11-2002
			PL	342473 A1	04-06-2001
			SK	10312000 A3	07-11-2000
			WO	9936104 A2	22-07-1999
			US	2001003580 A1	14-06-2001
			US	2004057991 A1	25-03-2004
			ZA	9900247 A	14-07-2000
US 2002102217	A1	01-08-2002	US	6331289 B1	18-12-2001
			AT	249247 T	15-09-2003
			AU	733477 B2	17-05-2001
			AU	4718297 A	22-05-1998
				733495 B2	17-05-2001
			AU		
			ΑU	4786697 A	22-05-1998
-			AU AU	4786697 A 4786797 A	22-05-1998 22-05-1998
			AU AU AU	4786697 A 4786797 A 4786897 A	22-05-1998 22-05-1998 22-05-1998
·			AU AU	4786697 A 4786797 A	22-05-1998 22-05-1998

Information on patent family members

ional Application No
IB2004/000243

		15204/000243		
Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 2002102217 A1		BG	103438 A	31-01-2000
		BG	103439 A	31-01-2000
		BR	9712683 A	19-10-1999
		BR	9713978 A	02-05-2000
		CA	2269985 A1	07-05-1998
		CA	2270120 A1	07-05-1998
		CN	1440816 A	10-09-2003
		CN	1238700 A	15-12-1999
		CN	1234742 A	10-11-1999
		CZ	9901494 A3	15-09-1999
•		DE	69724817 D1	16-10-2003
		DE	69724817 T2	01-07-2004
		EP	1007101 A2	14-06-2000
		EP	0973552 A2	26-01-2000
		EΡ	0991427 A2	12-04-2000
		ĒΡ	0971747 A2	19-01-2000
•		EP	0946202 A2	06-10-1999
		EP	0963209 A2	15-12-1999
•		ES	2206689 T3	16-05-2004
		WO	9818500 A2	07-05-1998
•		WO	9818501 A2	07-05-1998
		WO	9818495 A2	07-05-1998
		WO	9818496 A2	07-05-1998
		WO	9818497 A2	07-05-1998
		WO	9818498 A2	07-05-1998
		HU	0000357 A2	28-06-2000
		JP	2001511765 T	14-08-2001
		JP	2001503407 T	13-03-2001
		JP	2002515889 T	28-05-2002
		JP	2001502719 T	27-02-2001
		KR	2000052829 A	25-08-2000
		KR	2000052830 A	25-08-2000
		NO	991889 A	28-06-1999
		NO	991890 A	28-06-1999
		NZ	335596 A	27-10-2000
		NZ	335799 A	24-11-2000
		US	6264914 B1	24-07-2001
	•	US	6051207 A	18-04-2000